IAP5 Rec'd PCT/PTO 30 AUG 2006

10/591150

Saline-Enhanced Catheter for Radiofrequency Tumor Ablation

The present invention relates to a device and method for thermal treatment of tissue, in particular for destroying tumors.

Thermal damage of undesired cells for tumor ablation by application of a high frequency electromagnetic field with a needle electrode is well known. The use of alternating current at frequencies greater than 10 kHz thermally excites the tissue molecules without causing pain or muscular contractions. At frequencies exceeding 900 MHz, heat dissipation is hard to control in view of the greater capacitive effects at these high frequencies. The working range of radiofrequency (RF) systems thus lies within the range of 10 kHz to 900 mHz.

Heating tissues to more than 50 °C leads to the breakdown of proteins and cellular membranes, which results in cellular death. The use of RF interstitial thermoablation to destroy tumors is dependent on the physician's ability to insert the needle-electrode into the tumor under ultrasound or computed tomographic guidance. Recently, there has been marked interest in image-guided RF tumor ablation as a minimally invasive thermal therapy, especially for focal metastasic and primary liver tumors, given the significant morbidity and mortality of standard surgical resection and the large number of patients that cannot tolerate such radical surgery.

In the most commonly used monopolar electrode configurations, current flows from an electrosurgical probe in the form of a small active electrode through the tissues to a grounding electrode usually placed on the patient's thigh or back. In these conventional RF ablation devices, the current delivered to the tissue adjacent to the active electrode is proportional to $1/r^2$ from the electrode center, and the developed heat from translational molecular motion (ohmic or resistive heating) occurs in a very narrow rim around the electrode (proportional to $1/r^4$). The heat generated immediately adjacent to the electrode propagates through the tissue by thermal conduction. This implies a rapid rise of temperature to

greater than 100°C at the tissue-electrode interface, which causes desiccation and coagulum formation. Desiccated cellular tissues adhere to the electrode and form an electrically insulating coating resulting in a rapid and significant increase of impedance around the electrode with a subsequent power "roll-off". This effect precludes further RF energy conduction beyond the desiccated tissue and halts further tissue coagulation. Furthermore, blood flowing within the vessels acts as a heat sink and substantially limits the necrotizing effect of RF treatment in the adjacent tissue. Existing technology is limited in that only 3.5 to 4 cm diameter (about 33 cm^3 of tissue volume) may be ablated in a single cycle. Therefore, to treat tumors larger than 2.5 cm in diameter, including at least 1 cm margin of healthy tissue rim, multiple overlapping ablations are required to encompass the tumor and the surrounding healthy tissue rim. Conventional methods are thus tedious and need to be performed with great precision.

One way to partly solve the problem of the monopolar mode that arises from the disadvantageous electric field distribution is to use the bipolar mode where the probes are both active and placed close to each other in the liver. However, only a slight increased lesion size can be obtained because of the above-mentioned phenomenon of increased impedance around the electrodes. Thus the lesions may never become confluent if the electrodes are separated more than 2-3 cm.

Another potential strategy to increase the efficacy of RF ablation is to infuse NaCl solutions into the tissue through an active electrode. Two reasons have been provided to explain the improved tissue heating and increased RF-induced coagulation with simultaneous saline infusion: (a) that NaCl alters electrical conductivity of the tissue to permit greater RF energy deposition, or (b) that the infusion of fluid during RF application improves the thermal conduction within the tissues by more rapidly and effectively convecting heat over a larger tissue volume avoiding the desiccation of the tissue around the electrodes at the same time. It has however been observed that monopolar saline-enhanced electrodes

form irregularly shaped areas of coagulation with limited control of lesion size. With this method as in any monopolar method the current has to flow from a small active electrode with a small surface and high impedance, through the body to a much larger electrode often referred to as a "return electrode" placed on the patient's thigh or back. During the infusion of saline solution, the active electrode may be connected to the return electrode with a very large number of possible electric field lines, whereby RF energy can be dissipated at various undetermined distances from the active electrode. This could be an explanation for the lack of predictability of the lesions achieved with this method. Furthermore, with the conventional application of a saline-enhanced electrode in a monopolar way a dangerous reflux of heated saline solution through the puncture and extended to the biliary system have been observed, leading to some severe complications.

Considering the aforegoing, an object of this invention is to provide a device for thermal ablation of tissue enabling good control, predictability and regularity of the lesion shape. Moreover, operation and performance of the device should be highly reliable.

It is an advantage to provide a device for thermal ablation of tissue that is capable of treating a large volume of tissue in a single cycle.

It is an advantage to provide a device for thermal ablation of tissue that does not require a very high degree of precision, thereby facilitating operations, improving the quality of treatment, and reducing the risk of error and the implications of insufficiently precise manipulations.

Objects of this invention have been achieved by providing a device for thermal ablation of tissue according to claim 1, and a method of thermal ablation of tissue according to claim 10.

Disclosed herein is a catheter for the radiofrequency ablation of tissue, the catheter comprising at least one pair of electrodes adapted to function in bipolar mode, each electrode of the pair comprising supply channels adapted for the perfusion of saline solution around the electrodes, the catheter further comprising at least two end electrodes arranged towards opposed ends of the catheter on either side of the pair of bipolar electrodes, said end electrodes adapted to function in monopolar mode. A third monopolar electrode may advantageously be positioned between the pair of bipolar electrodes.

One of the functions of the monopolar electrodes is to seal the puncture performed by the catheter to better contain and control the perfusion of saline solution around the bipolar electrodes.

As each of the bipolar electrodes has its own saline solution supply channels, these may be independently supplied with saline solution, thus enabling a precise and predictable control of the lesion shape, in conjunction with the sealing of tissue around the catheter extremities and between the bipolar electrodes. The bipolar electrode configuration in the saline solution perfusion enables a better control and focus of the radiofrequency energy between the electrodes and is less sensitive than monopolar configurations to an uneven diffusion of saline solution, since the saline solution further away from the two electrodes will not dissipate RF energy as much as the solution close the electrodes. Furthermore in the bipolar mode the electric field gradient does not drop as sharply as in the monopolar mode and also stays fairly constant in the region between the probes. This advantage also becomes apparent when comparing the temperature distributions of the alternating monopolar mode and the bipolar modes.

Trials using two probes both perfused with independent pumps with a solution of NaCl show that it is possible to perform homogeneous and significant heating in the area of the tissue between the two probes regardless of the distance between them, on condition that the influence of blood cooling is limited. Thus

predictable ellipsoids of coagulation necrosis in a large range of sizes can be generated with the device according to the present invention.

Advantageously, a device for the thermal ablation of tissue according to this invention enables the creation of a relatively large lesion with a regular shape, while eliminating overheating at the tissue-electrode interface and producing an approximately uniform temperature throughout the volume of tissue being treated. This overcomes the complications related to conventional devices and treatment methods.

The outlets of the saline solution supply channel in the bipolar electrodes are arranged at a small distance from respective extremities of the bipolar electrodes, the distance being sufficient to avoid obstruction by the coagulation effected by the monopolar electrodes.

The size of the lesion to be created will depend on the length of the catheter in the present invention, which can be easily adapted by providing longer or shorter bipolar electrodes and to some extent by adapting the length of the dielectric and of the central monopolar electrode separating the bipolar electrodes.

Thermal ablation of tissue with a device according to this invention may be performed according to the following procedure. The catheter is inserted into the patient's tissue and guided to the tumor or volume of tissue to be destroyed, with the assistance of an ultrasound or computer tomographic guidance apparatus, as performed in conventional treatments. Once in place, the monopolar electrodes are energized with radiofrequency electrical current, without a saline solution, to seal the punctured tissue around the monopolar electrodes. Subsequently, saline solution is pumped through the bipolar electrode supply channels into the tissue surrounding the electrodes, and the bipolar electrodes are supplied with radiofrequency alternating current to perform the thermal ablation of tissue. Voltages may be registered using an

oscilloscope or similar equipment connected to the bipolar electrodes, and thermocouples mounted in the catheter connected to a temperature acquisition unit may be used to monitor the temperature at various positions along the catheter.

The thermocouples may advantageously be slidably mounted in the catheter and insertable a certain depth in the tissue surrounding the catheter in order to better measure the temperature in the tissue during treatment, and thus control of the amount of energy supplied and the duration of the operation.

Further advantages and aspects of the invention will be apparent from the claims and following description of an embodiment of the invention and the appended drawings, in which

Fig. 1 is a cross-sectional view illustrating an embodiment of a catheter according to this invention;

Fig. 1a is a detailed cross-sectional view of the part of the cathether IA shown in Fig. 1;

Fig. 2 is a simplified schema illustrating a system for thermal ablation of tissue connected to a device with catheter according to this invention.

Referring to the figures, a device 1 for thermal ablation of tissue, in the form of a catheter, with a long tubular shape extending from a pointed piercing or insertion tip 2 to a rear end 3 is shown. The diameter D of the catheter is preferably less than 3 mm in order to reduce the size of the puncture and adverse effects related thereto. The overall length of the catheter according to this invention will depend on the volume of the lesion to be created, whereby the length of the catheter is selected to be approximately equivalent to the size of the desired lesion. In the case of a tumor of say 6 cm in diameter, the

selected length of the active part of the catheter will for example lie in the range of 7 to 9 cm.

The catheter comprises a pair of electrodes 4, 5 adapted to function in a bipolar manner (hereinafter "bipolar electrodes"), in the form of tubular metal elements arranged in a juxtaposed manner on a common axis and separated electrically by one or more dielectric elements 6, 7 from each other and with respect to a central electrode 8 adapted to function in a monopolar mode (hereinafter "central monopolar electrode"). Monopolar electrodes are also provided at extremities of the catheter, a rear monopolar electrode 9 separated from one of the bipolar electrodes 5 by an insulating element 10 and a front monopolar electrode 11 separated from the bipolar electrode 4 by an insulating element 12. The front monopolar electrode 11 may be shaped so as to form the pointed piercing tip of the catheter.

The catheter further comprises a plurality of liquid supply channels for perfusion of saline solution into the tissue surrounding the catheter. The supply channels are connected to outlets, for example in form of holes, feeding out of the periphery of the bipolar electrodes. Preferably, each bipolar electrode 4, 5 is provided with a supply channel with an outlet 14a, 14b, close to the center of the catheter, but arranged at a distance B sufficiently far from the central monopolar electrode 8 to avoid being obstructed by the coagulated tissue formed by the monopolar electrode during the initial phase of the operation. Each bipolar electrode also comprises preferably supply channel outlets 15a, 15b proximate outer ends of the bipolar electrodes, these outlets also preferably positioned at a distance B from respective monopolar end electrodes 9, 11 sufficient to avoid being obstructed by the coagulation around the outer monopolar electrodes. It is possible, within the scope of the invention, to provide further saline solution supply channels positioned and having outlets along the electrodes. One or more outlets may also be provided around the periphery of the catheter for each of the supply channels. In the configuration illustrated in Fig. 1, the central and outer supply channel outlets are preferably oriented in

opposed directions in order to ensure a homogeneous distribution of saline solution around the catheter.

The central and outer electrodes are advantageously supplied with independent supply systems, in particular independent pumps 18a, 18b, in order to enable the perfusion of saline solutions of different salt concentrations around the ends of the catheter in relation to around the center of the catheter. It is thus possible to supply the ends of the catheter with a saline solution (typically sodium chloride solution) with a higher concentration than the saline solution supplied through the central outlets 14a, 14b, so as to improve electrical current flow through parts of the tissue that are distant from the catheter, thereby improving control of the lesion 23 shape and volume. Positioning of the outlets 15b, 14b and 14a, 15a towards the ends of each bipolar electrode 4, 5 improves electrical current distribution due to the preferential dissipation of the RF current near the ends of the electrodes.

The catheter may advantageously also comprise a plurality of thermocouples 16 at positions along the catheter in order to control the temperature during operation, not only the overall temperature but also the temperature distribution along the catheter. The thermocouples may be connected to a temperature acquisition unit 19 for monitoring during operation. The thermocouples are advantageously slidably mounted in conduits 17 in the catheter, and may be inserted a certain depth into surrounding tissue during operation in order to measure the temperature in the tissue being treated. This allows for a better control of RF power to be applied, as well as the duration of thermal treatment.

Other monitoring apparatus such as voltage sensors 20 connected to the electrodes, the pump flow, and the RF generator 21 may be interconnected to a control unit 22, for example such as a personal computer for monitoring and controlling parameters during operation.

The operation steps of the device according to this invention may be performed according to the following protocol. In the initial steps, a catheter of the appropriate length is selected, which should be at least 1 cm longer than the unhealthy tissue to be destroyed, for example a tumor, in order to encompass the tumor safely with the lesion 23. The catheter is guided with the assistance of an imaging system, such as an ultrasound or computer tomographic guidance system as known in the art, into the patient's tissue 24. A grounding pad or return electrode with a large surface is positioned on the patient's skin in an appropriate position as is known in the art.

Power is then supplied to the monopolar electrodes for a time sufficient to perform the coagulation and sealing of tissue around the monopolar electrodes, for example a power of 60 W for 20 seconds.

After the sealing operation, power to the monopolar electrodes is switched off and power is supplied to the bipolar electrodes and saline solution is pumped with the separate pumps independently to the central, respectively outer outlets of the supply channels in the bipolar electrodes 4, 5. Preferably, the required volume of saline solution or a portion thereof is pumped into the lesion prior to application of power to the bipolar electrodes. For example, 100 ml of saline solution with for example a concentration of 3 % in salt for the central outlets, and 20 % for the peripheral or outer outlets of each electrode is infused.

RF ablation may then be started when a certain impedance is reached, for example 60 Ω at a power output of 1 W. The power supply during RF ablation may be successively increased, for example 30 W the first minute, 60 W the second minute, and 90 W the third minute, whereby the RF ablation and perfusion of saline solution may be stopped either when the desired lesion is achieved with the assistance of the image guidance system, or based on empirical values obtained from prior experimentation. The thermocouples, inserted into the surrounding tissue after the catheter is inserted in its position of operation, allows the temperature of the tissue being treated to be monitored,

thus providing information useful for control of the RF power and/or duration of treatment. Whereas the length of the thermal lesion will depend principally on the length of the catheter, the diameter of the generally ellipsoid-shaped lesion may be controlled by a combination of the concentration of the saline solution infused into the tissue and the power and duration of RF ablation. The thermocouples are retracted into the catheter after the end of treatment and prior to pulling the catheter out of the patient.

The catheter may advantageously be provided with a closed internal cooling circuit (not completely shown) connected to an inlet 26 and outlet 28 for a cooling fluid, that is preferably a physiological saline solution, to flow inside the catheter to cool the outer surface thereof. The cooling, in bipolar RF mode, participates in eliminating overheating at the tissue-electrode interface and in particular prevents coagulation and burning of tissue in contact with the catheter that may reduce conductivity and thus the effectiveness of the RF ablation treatment.

Claims

1. Catheter for the radiofrequency ablation of tissue, comprising at least one pair of bipolar electrodes adapted to function in bipolar mode, each bipolar electrode comprising supply channels adapted for the perfusion of saline solution around the electrodes, the catheter further comprising at least two end electrodes arranged towards opposed ends of the catheter, on either side of the pair of bipolar electrodes, said end electrodes adapted to function in monopolar mode.

2. Device according to claim 1, 2 or 3, wherein each bipolar electrode comprises at least two saline solutions supply channels (14a, 15a; 14b, 15b).

3. Catheter according to claim 1 or 2, wherein the liquid supply channels with outlets (15a, 15b) arranged proximate the front and rear ends of the catheter are supplied with the saline solution independently of liquid supply outlets (14a, 14b) arranged proximate the center of the catheter.

4. Device according to claim 1 or 2, further comprising a central electrode (8) arranged between the bipolar electrodes (4, 5), the central electrode adapted to function in monopolar mode.

5. Device according to any one of the preceding claims, further comprising one or more thermocouples (16), said thermocouples being retractably mounted in the catheter and actionable so as to be inserted into tissue surrounding the catheter.

6. Catheter according to any one of the preceding claims, wherein the liquid supply channel outlets are arranged at a distance (B) from the respective central and end monopolar electrodes, that is sufficient to avoid being in a region of coagulated tissue formed around said monopolar electrodes.

7. Apparatus for radiofrequency ablation of tissue comprising a catheter according to any one of the preceding claims and at least two independently controlled pumps for supplying saline solution to separate supply channels of each bipolar electrode.

8. Apparatus according to the preceding claim, further comprising a temperature acquisition unit connected to thermocouples of the catheter.

9. Apparatus according to either one of the two preceding claims, further comprising an RF generator, whereby the independently controlled pumps, RF generator, and temperature acquisition unit are connected to a computing unit, such as a PC, for monitoring and controlling operations.

10. Method of radiofrequency ablation of tissue, comprising the steps of :

- providing a catheter having at least one pair of bipolar electrodes with saline solution supply channels, and at least two monopolar electrodes arranged towards opposed ends of the catheter on either side of the pair of bipolar electrodes;

- inserting the catheter into a central region of the volume of tissue to be ablated;

- supplying electrical power to the monopolar electrodes to coagulate tissue therearound and seal the puncture performed by the catheter;

- perfusing saline solution into the tissue surrounding the bipolar electrodes and supplying electrical RF energy to the bipolar electrodes for thermal ablation.

11. Method according to the preceding claim, wherein the step of perfusing saline solution comprises supplying saline solution via supply channels (14a,

14b) arranged proximate the center of the catheter at a concentration lower than saline solution supplied to outlets (15a, 15b) arranged proximate opposed ends of the catheter.

12. Method according to either one of the two preceding claims, wherein prior to or during the step of operation of the bipolar electrodes, retractable thermocouples (16) mounted in the catheter are inserted at a certain depth into the surrounding tissue.

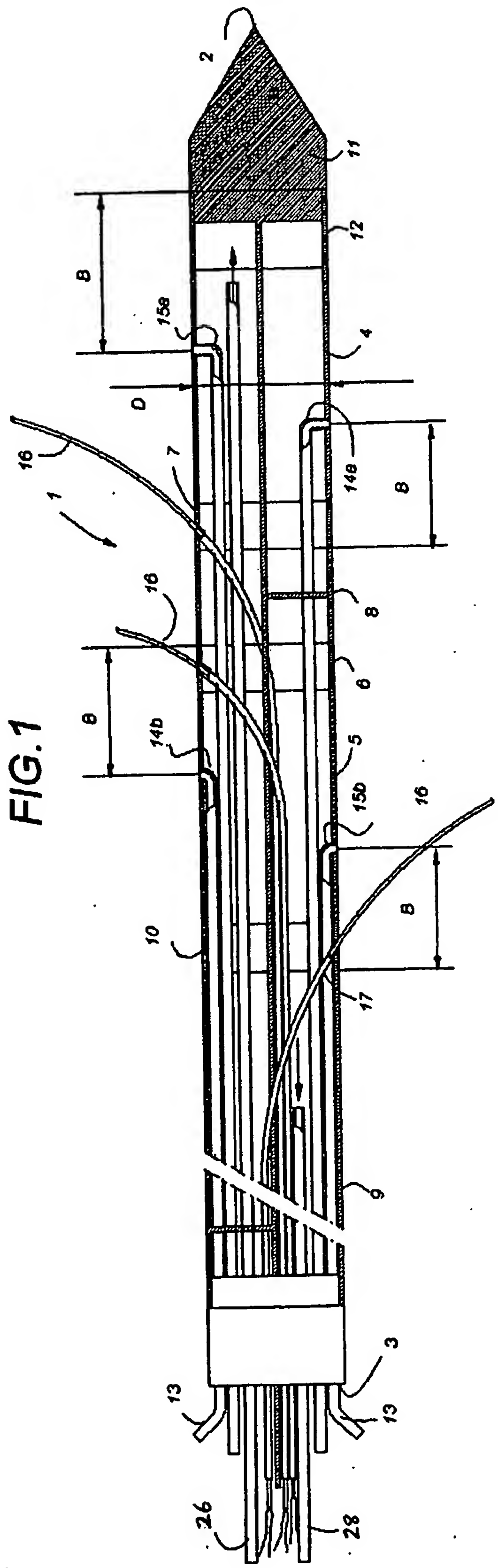

FIG.1

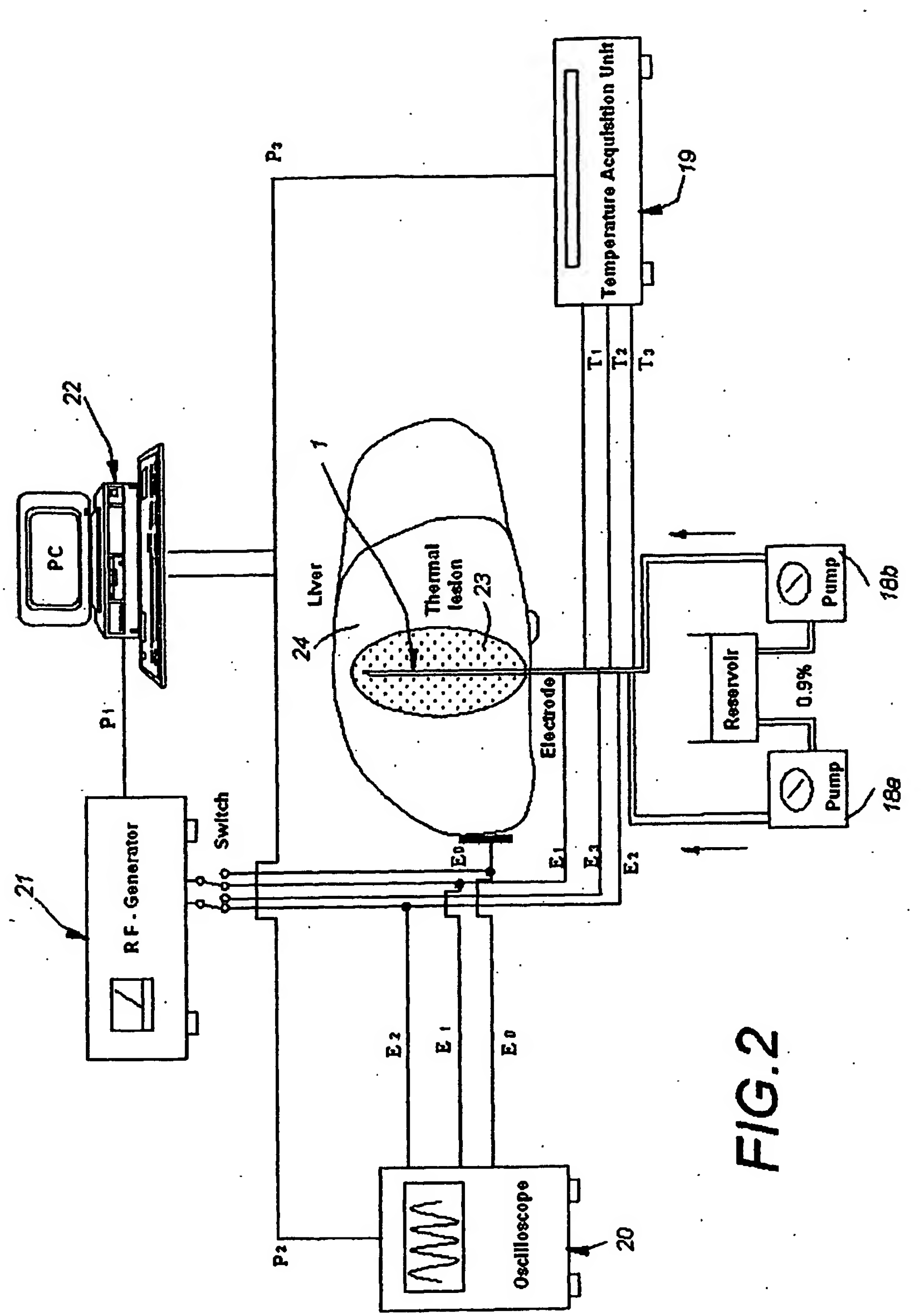
Temperature Acquisition Unit
19
P3
PC
22
P1
R F - Generator
21
Switch
Liver
Thermal lesion
23
24
1
Electrode
T1
T2
T3
Reservoir
0.9%
Pump
18b
Pump
18a
E0
E1
E3
E2
E2
E1
E0
Oscilloscope
20
P2

FIG.2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/000564

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B18/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 208 881 B1 (CHAMPEAU EUGENE J) 27 March 2001 (2001-03-27) column 3, lines 30-35; figures 1-3 column 4, line 41 - column 5, line 6 column 7, line 63 - column 8, line 30 column 9, lines 1-5	1-4,6,7, 9
Y		5,8
Y	US 2002/107512 A1 (EDWARDS STUART D) 8 August 2002 (2002-08-08) paragraphs '0096!, '0097!; figure 29	5,8
X	US 6 579 288 B1 (SWANSON DAVID K ET AL) 17 June 2003 (2003-06-17) column 9, line 59 - column 11, line 5 column 15, line 61 - column 17, line 6 figures 1,2	1,5,7,8

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 May 2005	19/05/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Jonsson, P.O.

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/25917 A (EP TECHNOLOGIES, INC) 24 July 1997 (1997-07-24) abstract; figures 1-4 page 14, line 26 - page 15, line 27 page 17, line 16 - page 18, line 22	1,5,7,8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/000564

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10-12
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB2005/000564

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6208881 B1	27-03-2001	US 6400976 B1	04-06-2002
US 2002107512 A1	08-08-2002	US 6056744 A	02-05-2000
		US 2004147921 A1	29-07-2004
		AU 3672299 A	16-11-1999
		WO 9955245 A1	04-11-1999
		AT 287242 T	15-02-2005
		AU 752243 B2	12-09-2002
		AU 2778899 A	06-09-1999
		CA 2319517 A1	26-08-1999
		DE 69923291 D1	24-02-2005
		EP 1056403 A1	06-12-2000
		JP 2002503512 T	05-02-2002
		WO 0176495 A1	18-10-2001
		WO 9942044 A1	26-08-1999
		US 6254598 B1	03-07-2001
		US 2002072738 A1	13-06-2002
		US 6315776 B1	13-11-2001
		US 2004082950 A1	29-04-2004
		US 2001034518 A1	25-10-2001
US 6579288 B1	17-06-2003	US 6464699 B1	15-10-2002
		US 6142994 A	07-11-2000
		US 6152920 A	28-11-2000
		AT 256996 T	15-01-2004
		AU 8979301 A	13-03-2002
		CA 2420513 A1	07-03-2002
		DE 60101685 D1	05-02-2004
		DE 60101685 T2	09-12-2004
		WO 0217804 A2	07-03-2002
		EP 1313404 A2	28-05-2003
		ES 2211826 T3	16-07-2004
		JP 2004507314 T	11-03-2004
		US 2003014048 A1	16-01-2003
		US 2002026187 A1	28-02-2002
		AU 5621001 A	08-10-2001
		WO 0172231 A2	04-10-2001
		CA 2305525 A1	22-04-1999
		DE 69807248 D1	19-09-2002
		DE 69807248 T2	17-04-2003
		DE 69827978 D1	05-01-2005
		EP 1224917 A2	24-07-2002
		EP 1024761 A2	09-08-2000
		JP 2001519199 T	23-10-2001
		WO 9918878 A2	22-04-1999
		US 2002151889 A1	17-10-2002
		US 2003014049 A1	16-01-2003
		US 6468272 B1	22-10-2002
		US 6645200 B1	11-11-2003
		US 6610055 B1	26-08-2003
		US 6464700 B1	15-10-2002
		US 6425895 B1	30-07-2002
		US 2004049182 A1	11-03-2004
		US 2005015083 A1	20-01-2005
		US 2005033285 A1	10-02-2005
		ES 2181289 T3	16-02-2003
WO 9725917 A	24-07-1997	US 5836874 A	17-11-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB2005/000564

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9725917 A		CA 2243481 A1	04-12-1997
		CA 2243595 A1	24-07-1997
		EP 0879015 A1	25-11-1998
		EP 0975386 A1	02-02-2000
		JP 2000504242 T	11-04-2000
		JP 2002528039 T	27-08-2002
		US 6099526 A	08-08-2000
		WO 9725916 A1	24-07-1997
		WO 9725917 A1	24-07-1997
		WO 9725918 A1	24-07-1997
		WO 9725919 A1	24-07-1997
		WO 9725929 A1	24-07-1997
		WO 9745156 A2	04-12-1997
		US 2003093069 A1	15-05-2003
		US 6179835 B1	30-01-2001
		US 5925038 A	20-07-1999
		US 5846238 A	08-12-1998
		US 5871483 A	16-02-1999
		US 5853411 A	29-12-1998
		US 5891135 A	06-04-1999
		US 5891136 A	06-04-1999
		US 5961513 A	05-10-1999
		US 2001025175 A1	27-09-2001
		US 6357447 B1	19-03-2002
		US 6475213 B1	05-11-2002
		US 5991650 A	23-11-1999